continuation or divisional applications, under 35 U.S.C. §121, relating to the subject matter of the cancelled claims.

A marked up copy of the amended claims is attached.

REMARKS

The Official Action dated June 26, 2002, has been carefully considered. In view of the foregoing amendments and these remarks, favourable reconsideration and allowance of this application are respectfully requested.

The June 26, 2002 Official Action repeats and makes final the Restriction Requirement raised in the previous Official Action. Consequently claims 42-63, 68-70, 72-74, 77-94 and 96-101 are withdrawn from consideration.

An abstract on a separate sheet is required.

The Examiner requires the amendment of the first page of the description to refer to Applicants' underlying PCT application.

A rejection has been raised under 35 U.S.C. § 112, first paragraph, against the phrase "substantially free of sequences which are not part of said at least one MHC-binding epitope of Tek", which allegedly constitutes new matter. Consequently, all claims under consideration are rejected.

All claims under consideration stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not meeting the written description requirement.

All claims under consideration stand rejected under 35

U.S.C. § 112, second paragraph, as allegedly being indefinite.

All claims under consideration stand rejected under 35 U.S.C. § 102(b), as allegedly being anticipated by Breitman et al., as evidenced by Rammensee et al..

The above listed rejections constitute the entirety of the grounds set forth in the Official Action dated June 26, 2002, for refusing allowance of this application.

In accordance with the present amendment, an Abstract is provided herewith on a separate sheet and the first line of the specification has been amended to refer to the PCT application from which this application is derived. Also in accordance with this amendment, the peptide claims (claims 42-53) have been amended to refer to a "peptide", rather than a "peptide fragment". Support for this amendment comes *inter alia* from the claims as filed. Similarly, the term "consisting essentially of" has been re-introduced into claim 42. Basis for this amendment also comes from the claims as filed. Claim 42 has also been amended to specify that "Tek protein" is that having the amino acid of Fig. 1 (SEQ ID NO. 1). Basis comes *inter alia* from references throughout the specification to Fig. 1 showing the sequence of Tek. See e.g. the legend for Fig. 1 on page 28, at line 24: "Figure 1. Shows the sequence of Tek …".

The subject matter of claims 64 and 65 has been split up into two sets of two claims, resulting in new claims 102 and 103.

Claim 90 has been amended to introduce language from

a deleted claim to which it previously referred.

Entry of the present amendment is respectfully requested. No new matter has been introduced into the application by reason of any of the amendments presented herewith.

Each of the grounds of rejection set forth in the June 26, 2002 Office Action is believed to be inapplicable to the claims as presently amended and is, therefore, respectfully traversed for the reasons set forth below.

Turning first to the Restriction Requirement that has been made final, Applicants have limited the claims to the following Groups of inventions, as identified in the original Restriction Requirement dated February 15, 2002, namely:

Group I (claims 42-53 and 80, drawn to peptides),

Group IX (claims 64-67, 71, 75, 76 and 95, which are currently under consideration, drawn to nucleic acids encoding peptides),

Group XV (claims 72-73, drawn to a method of making a nucleic acid), and

Group VIII in part (claim 90, drawn to a method of making a vaccine using a nucleic acid)

The Examiner upheld and made final the Restriction Requirement, on the basis of comments that relate to antibodies. Those comments are now moot in light of the deletion of all claims pertaining to antibodies. The Examiner made no reference, however, to various other grounds of traversal of the original

Restriction Requirement that were included in Applicant's response of April 15, 2002 thereto (paper no. 10).

In particular, the Examiner's attention is respectfully directed to two specific grounds of traversal set out in that response. Firstly, the M.P.E.P. expressly permits the inclusion of independent claims to a product, a method specifically adapted for the manufacture of the product and a use of the product (§1850(b), cited in Applicant's response of April 15). The above-identified claims of Groups XV and VIII (in part) relate respectively to methods of manufacturing and using the nucleic acid products of Group IX, the provisionally elected invention. Accordingly, Applicants respectfully submit that restriction between these groups is inappropriate.

Secondly, the PCT Administrative Instructions expressly state that unity of invention exists between a protein and a nucleic acid that encodes the protein (Example 17). The above-identified claims of Group I relate to peptides encoded by the nucleic acid of Group IX. Accordingly, Applicants respectfully submit that restriction between these groups is inappropriate.

Applicants therefore respectfully request favourable reconsideration of the Restriction Requirement, insofar as it requires restriction between the above-identified groups of claims. Applicants further request that the withdrawal of claims 42-53, 72-73, 80 and 90 from consideration be reversed.

Regarding the first rejection under 35 U.S.C. §112, first paragraph, the Examiner considers the phrase in claim 42

"substantially free of sequences which are not part of said at least one MHC-binding epitope of Tek" to be inadequately supported in the specification. The Examiner consequently considers that claim 64, which refers to claim 42, does not meet the written description requirement of §112 and that it contains new matter. Claim 42 has been amended to more closely track claim 1 as originally filed, by including the feature that the peptide consists essentially of at least one epitope. The feature "substantially free of sequences which are not part of said at least one MHC-binding epitope of Tek" is retained and further limited, to add further clarification to the claim.

In this connection, Applicants refer the Examiner to the first paragraph on page 4 of the specification, which reads:

> 'By the terms "consists essentially of", it is intended to mean that peptides or polypeptides of the present invention consist largely of one or more sequences which represent epitopes of Tek protein, with little in the way of other sequences of the native Tek protein.'

Applicants respectfully submit that this paragraph provides clear basis for the phrase "substantially free of sequences which are not part of said at least one MHC-binding epitope of Tek". Applicant therefore respectfully requests reconsideration and withdrawal of this rejection.

As for, the second rejection under 35 U.S.C. §112,

first paragraph, it is the Examiner's position that the specification does not provide adequate written description of the claimed invention. This rejection, arises because the application relates to human Tek, whereas the claims are not so limited. The claims have now been limited to recite the Tek protein of Fig. 1 (SEQ ID NO. 1), thus overcoming this rejection.

Further, the Examiner alleges at page 4 of the June 26, 2002 Office Action that "[t]he specification only provides the identity of three or four peptides which bind a single class I allele (HLA-A2), and stimulate T cell proliferation (e.g. are immunogenic). The specification also appears to disclose four peptides which bind several different class II (HLA-DR) alleles. However, the art recognises that there are hundreds of MHC class I and II alleles in humans wherein said molecules bind different and largely nonoverlapping sets of peptides derived from the same protein. Thus the written description is not commensurate with the scope of the claimed inventions."

Applicant respectfully points out, however, that this objection does not take into account the teaching provided in Figs 1 and 2, which represent the raw data from which the specifically exemplified peptides were derived. This data provides a more comprehensive analysis of the sites of putative T cell epitopes in the Tek protein of Fig. 1. From this data, ten peptides were generated and assayed for binding to HLA-A2 and nine were positive (Table 1, page 33). Eight of these nine

showed moderate to strong binding, with five showing strong binding (page 33, lines 21-27). Of these, three were selected for further study and gave rise to positive results in the human T cell proliferation assay, singly and in combination (Table 3, page 35).

Applicant respectfully submits, therefore, that the "three or four peptides" acknowledged by the Examiner are not the only teaching in the specification. The specification provides much more comprehensive teaching of possible and likely MHC-binding epitopes, of which the three or four peptides acknowledged by the Examiner are merely those which have been studied in most depth. Reconsideration and withdrawal of this rejection is, therefore, respectfully requested.

Turning attention now to the rejection under 35 U.S.C. § 112, second paragraph, the Examiner considers that the claims under consideration are indefinite. The first part of the rejection concerns the reference in claim 64 to non-elected claim 42. As indicated above, however, the withdrawal from consideration of claim 42 has been traversed. Applicant therefore respectfully requests reconsideration of this part of the rejection on the basis that under well established United States Patent and Trademark Office guidelines claim 42 should not have been withdrawn from consideration.

The second part of the §112, second paragraph rejection is that claims 64 and 65 recite different products, namely a recombinant DNA construct and a recombinant virus vector. These

claims have been split into separate pairs of claims: claims 64 and 65 for a recombinant DNA construct and new claims 102 and 103 for a recombinant virus vector. Reconsideration and withdrawal of this part of this rejection is, therefore, respectfully requested.

The third and final part of this rejection concerns the phrase "substantially free of sequences which are not part of said at least one MHC-binding epitope of Tek". The Examiner considers that it is not clear how many residues outside the MHC-binding epitope(s) may be encompassed by the claim. Applicants respectfully point out that this will not be an absolute figure, but is relative. The specification discloses that the peptides of the invention "consist largely of one or more sequences which represent epitopes of Tek protein, with little in the way of other sequences of the native Tek protein" (see page 4, lines 3-7). This clearly requires that a majority of the amino acid residues of a peptide of the invention are within such epitopes, and only a minority of the amino acid residues lie outside such epitopes. Thus, the exact number of "non-epitope" residues that can be accommodated in a peptide of the invention will depend on the number and size of the epitopes in the peptide: a peptide comprising a single MHC-binding epitope of, say, 9 residues could accommodate, say, 5 non-epitope residues within the above guidance. It could not, however, accommodate 50 residues. By contrast, a peptide comprising two non-overlapping epitopes each of 9 residues could accommodate more non-epitope residues.

Applicants therefore submit that the guidance provided at page 4, lines 3-7 of the description is adequate to allow the skilled person to ascertain whether a peptide is substantially free of sequences which are not part of said at least one MHC-binding epitope of Tek. Applicant therefore requests reconsideration and withdrawal of this final part of the indefiniteness rejection.

Turning finally to the rejection under 35 U.S.C. § 102(b), the Examiner considers that claims under consideration to be anticipated by Breitman et al., as evidenced by Rammensee et al.. The line of reasoning advanced by the Examiner is that Breitman et al. discloses nucleic acids encoding fragments of Tek. In particular, Breitman et al. discloses a nucleic acid encoding a fragment consisting of the C-terminal 43 residues of Tek. The Examiner alleges in light of Rammensee et al. that such a fragment would inherently have MHC-binding capacity. In particular, the Examiner cites the disclosure in Rammensee et al. of the anchor residues of HLA-B*2705. These are shown on page 200. The Examiner further assumes that the phrase "substantially free of sequences which are not part of said at least one MHC-binding epitope of Tek" means not containing a large majority of the non-MHC binding amino acids found in intact Tek.

Applicants respectfully submit, however, that the Examiner's interpretation of "substantially free …" is directly at odds with that put forward in Applicants' specification. The Examiner is comparing the number of non-MHC residues in a

putative peptide of the invention with the total number of such residues in intact Tek. This is clearly not the intended meaning. The specification describes peptides of the invention as consisting largely of epitopes and having little in the way of other sequences of native Tek. These terms clearly relate to proportion of the residues in the peptide, not the total number of residues in native Tek.

In view of the absence of any disclosure in Breitman et al. and/or Rammensee et al. that the C-terminal 43 amino acids of Tek comprise a majority of residues that are in epitopes, and only a minority that are not, Applicants therefore submit that Breitman et al. does not disclose a peptide or nucleic acid having all the features of the instant claims. Accordingly, applicant requests reconsideration and withdrawal of this rejection also.

Furthermore, Applicants vigorously dispute the Examiner's allegation that the disclosure in Rammensee of the anchor residues for HLA-B*2705 demonstrates that the C-terminal 43 amino acids of Tek would inherently comprise an MHC-binding epitope. This allegation is presumably made on the basis that this amino acid fragment includes the amino acids R and L separated by six amino acids. This motif is found at positions 1076 to 1083 of SEQ ID NO. 1 of the present application, and corresponds to the anchor residues for HLA-B*2705 as disclosed on page 200 of Rammensee et al.. As indicated in the present specification, however, anchor residues are necessary but not

sufficient for MHC binding. Rather, non-anchor residues also exert significant effects (see page 30, lines 11-15). The Examiner will appreciate that the non-anchor residues in this motif (namely PSFAQI), with the exception of one (namely A) do not appear in the lists of preferred non-anchor residues for HLA-B*2705. Thus there is little likelihood that this motif represents an HLA-B*2705 epitope.

Applicants believe that the present amendment and request for reconsideration is fully responsive to the Official Action of June 26, 2002. In view of the foregoing amendments and remarks, it is respectfully urged, that all of the rejections set forth in the June 26, 2002 Office Action be withdrawn and that this application be passed to issue, and such action is earnestly solicited.

Respectfully submitted,

Patrick J. Hagan
Reg. No. 27,643
Attorney for Applicant

PJH:ksk

Marked-Up Version of Amended Claims

42. (Amended) An isolated peptide [fragment comprising] consisting essentially of at least one human MHC-binding epitope of the Tek protein having the amino acid sequence of Fig. 1 (SEQ ID NO. 1), the peptide [fragment] being substantially free of sequences of native human Tek protein which are not part of said at least one MHC-binding epitope of Tek, which isolated peptide [fragment] can stimulate an immune response.

43. (Amended) An isolated peptide [fragment] according to claim 42 comprising a single MHC-binding epitope of Tek protein.

44. (Amended) An isolated peptide [fragment] according to claim 42 comprising two or more MHC-binding epitopes of Tek protein.

45. (Amended) An isolated peptide [fragment] according to claim 44 wherein the amino acid sequence is such that the said two or more epitopes are contiguous or substantially contiguous.

46. (Amended) An isolated peptide [fragment] according to claim 44 wherein the amino acid sequence is substantially free of the amino acid sequence that occurs between neighbouring epitopes in the native full-length Tek protein.

47. (Amended) An isolated peptide [fragment] according to claim 42 wherein said at least one MHC-binding epitope comprises an amino acid sequence which appears within an amino acid sequence region selected from TEK1 (amino acids 55 to 90), TEK2 (amino acids 163 to 176), TEK3 (amino acids 345 to 362), TEK4 (amino acids 427 to 442) and/or TEK5 (amino acids 530 to 542) of the Tek polypeptide as shown in Fig. 1, or a corresponding region in a variant form of Tek, which is functionally homologous to the region shown in Fig. 1.

48. (Amended) An isolated peptide [fragment] according to claim 47, wherein said at least one MHC-binding epitope comprises an amino acid sequence having greater than 70% amino acid sequence identity with the amino acid sequence region selected from TEK1, TEK2, TEK3, TEK4 and/or TEK5 of the Tek polypeptide as shown in Figure 1.

49. (Amended) An isolated peptide [fragment] according to claim 42 which comprises one or more of the epitope sequences Z1, Z2, Z3, Z5, Z6, Z7, Z8, Z9, Z11, Z12 and Z32 as set forth in Tables 1 and 4, and, optionally, at least one of a variant form of said Z epitope sequences which is functionally homologous to a sequence shown in Tables 1 or 4.

50. (Amended) An isolated peptide [fragment] according to claim 42 which binds HLA-A2 with a stabilisation ratio of 1.3 or greater.

51. (Amended) An isolated peptide [fragment] according to claim 50 which can stimulate T cell proliferation.

52. (Amended) An isolated peptide [fragment] according to claim 50 which binds HLA-A2 with a stabilisation ratio of 1.5 or greater.

53. (Amended) An isolated peptide [fragment] according to claim 50 which binds HLA-A2 with a stabilisation ratio of 2.3.

64. (Amended) A recombinant DNA construct [or virus vector] which comprises a nucleic acid sequence encoding a peptide [fragment] according to claim 42.

65. (Amended) A recombinant DNA construct [or virus vector] according to claim 64 which has one or more regulatory sequences for controlling the expression of said peptide [fragment].

67. (Amended) A host cell containing and capable of expressing a nucleic acid encoding a peptide [fragment] according to claim 42.

71. (Amended) An isolated nucleic acid molecule encoding a peptide [fragment] of claim 42.

72. (Amended) A method of obtaining a nucleic acid molecule encoding a peptide [fragment] of claim 42, the method including hybridising a probe having a sequence encoding a peptide [fragment] of Tek regions TEK1 to 5 or a peptide [fragment] as identified in Tables 1 and 4, or a complementary sequence thereof, to target nucleic acid.

80. (Amended) An isolated peptide [fragment] according to claim 42, comprising one or more of the epitope sequences Z1, Z2, Z3, Z5, Z6, Z7, Z8, Z9, Z11, Z12 and Z32, as set forth in Tables 1 and 4, and at least one of a variant form of said Z epitope sequences which is functionally homologous to a sequence shown in Tables 1 or 4.

90. (Amended) A method of preparing a pharmaceutical composition [according to claim 88,] <u>for use as a vaccine to target endothelial cells lining the blood vessels of a tumour, said composition comprising a recombinant DNA construct or virus vector according to claim 64,</u> said method including the step of combining said recombinant DNA construct or virus vector with a pharmaceutically acceptable excipient, carrier, buffer or stabiliser.